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EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,175	PASZTY ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *13-42 and 46-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/05/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is response to Applicant's election of Group I, claims 1-12 and 43-45 drawn a nucleic acid molecule encoding a polypeptide, a vector, and a host cell. Election was made without traverse in the response filed on 11/12/03. Please note that the Office made a typographical error and included claim number 42 in Group I. Claim 42 belongs in Group II and thus will not be examined further. Therefore, claims 13-42 and 46-58 are withdrawn from further consideration because they are drawn to unelected inventions. However, Applicant has traversed the requirement for sequence election (SEQ ID NO: 1-23). The traversal is on the basis that there will be no hardship to the Office in performing a search with respect to the nucleotide sequences of SEQ ID Nos: 1, 4, 6, 9, 11, 14 and 16, because a search with respect to any one sequence would necessarily uncover all art that is pertinent to each of the other sequences. This is not found to be persuasive because as Applicant as indicated in pages 2 and 3 of the response of 11/12/2003 though the sequences have substantial identity they nevertheless encode proteins of different length. Therefore, LGR8 proteins (splice variants) containing these sequences are structurally and functionally different. Thus, the searches for each of the different sequences are not coextensive and would be a burden on the office to search all of the different sequences. Therefore, a LGR8 comprising SEQ ID NO: 1 will be searched. Thus, the restriction requirement is deemed proper and made FINAL.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

3. Claims 1-3 are objected to because of the following informalities: Claims also recite unelected inventions. Claims need to be rewritten reciting only the elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 and 43-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claims 1-3 recite " an nucleic acid which hybridizes under moderately or highly stringent conditions .....", moderately and stringent conditions are relative terms and renders the claim indefinite. Furthermore, some nucleic acids that might hybridize under conditions of moderate stringency, for example, would fail to hybridize at all under conditions of high stringency. The metes and bounds and bounds of the claim, thus cannot be ascertained. This rejection could be obviated by providing specific conditions supported by the specification that Applicants consider be "moderate or stringent." Claims 9-12 and 43-45 are rejected insofar as they depend on rejected claims 1-3.

4b. Claim 8 is indefinite because the claim recites a recombinant method for producing a polypeptide comprising insertion of the polynucleotide of claims 1-3 into a host cell. Claims 1(e), 2(f) and 3(h) recite nucleotide sequences that are complementary to nucleotide sequences. It is not clear how the polynucleotide complements of claims 1(d), 2(f) and 3(f) produce the polypeptide disclosed in the instant application. A complement is a sequence of nucleotide bases in one strand of a DNA or RNA molecule that is exactly complementary (adenine-thymine, adenine-uracil, or guanine-cytosine) to that on another single strand. Claims 9 and 10 are rejected insofar as they depend on rejected claim 8.

4c. Claim 8 is indefinite in that they only recite the polypeptide of interest by an arbitrary name. There is nothing in the claims that distinctly identifies the polypeptide. For example, others in the field may isolate and use the same protein, giving the said protein an entirely different name. Applicants should particularly point out and distinctly claim the "LGR8" polypeptide by sufficient identifying characteristics associated with the protein (e.g. amino acid sequence, molecular weight, etc.). Claiming biochemical molecules by a particular name given to the polypeptide by various workers in the field fails to distinctly claim what that protein is. There is no nexus between the DNA described in claims 1-3 and the LGR8 polypeptide of claim 8. It is not clear that they refer to the protein encoded by the nucleic acid. Also it appears that the nucleic acid is not required to encode the protein. Claims 9 and 10 are rejected insofar as they depend on rejected claim 8.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-12 and 43-45 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 1-12 and 43-45 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of the nucleic acid, the encoded protein or the significance of either.

It is clear from the instant specification that the "LGR8" protein encoded by SEQ ID NO: 1 described therein is what is termed an "orphan protein" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this protein, and the nucleic acid encoding it, may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be

potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to nucleotides encoding a protein of as yet undetermined function or biological significance. Applicant asserts that LGR8 can be used in the identification of modulators (paragraphs 0257 and 0258). It is also asserted that LGr8 could be used in gene therapy (paragraphs 0314-0322). There is absolutely no evidence of record or any line of reasoning that would support a conclusion that the "LGR8" protein of the instant application could be used in a methods of diagnosis, treatment, amelioration and/or prevention of diseases, disorders and conditions associated with LGR8 polypeptides (paragraph 0003-0004, 0329 and 0331-0342 of the specification). Applicant suggests that LGR8 polypeptides may be useful in diagnosing or treating diseases and conditions affecting skeletal muscle (paragraph 0332 and 0333), adrenal gland (paragraph 0334), testes (paragraph 0335), bone marrow (paragraph 0336), kidney (paragraph 0337), ovaries (paragraph 0338) and also play a

role in diseases associated with cell proliferation and differentiation (paragraphs 0339-0340). A role is also suggested in diseases and conditions that could be treated by decreasing cell proliferation and differentiation (paragraph 0340) Thus, it is claimed that LGR8 may be useful in the diagnosis and treatment of diseases such as muscular dystrophy, cachexia, miscarriage, endometriosis, uterine cancer, ovarian cancer, female infertility Cushing's disease, Addison's disease, male infertility, testicular carcinoma, leukemia, anemia, hypertension, low blood pressure, cancer, hyperplasia and hypertrophy (paragraphs 0332-0340). Neither the specification nor the prior art demonstrates a causal correlation or nexus of the claimed polypeptide with any of the conditions or disorders contemplated by the instant specification, therefore, there is no evidence of record that would provide for a method of treating/diagnosing any of the listed conditions or disorders. Accordingly, the skilled artisan would not consider such assertions to be substantial.There is absolutely no evidence of record or any line of reasoning that would support a conclusion that the "LGR8" protein of the instant application is involved in regulating growth and/or differentiation of any *particular* cell population. The record fails to indicate any evidence of any of these biological activities, and it would appear that until some actual and specific significance can be attributed to the protein identified in the specification as LGR8, the gene encoding it, or the antibody that binds it, the instant invention is incomplete. The specification asserts that the claimed protein will have activities similar to other LGR proteins based on amino acid sequence similarity, but it is not clear or predictive which activity of the LGR family will be possessed by the claimed protein based on structural similarity alone.

The protein of the instant specification is known to share structural similarity to the leucine-rich repeat-containing G-protein coupled receptor family of proteins which are known in the art to have biological significance similar to that of LH, FSH and TSH. These are possibly involved in the signal transduction pathway. LGR8 of the instant invention is identical to LGR8 described Hsu et al. (2002, post filing). See also the enclosed sequence comparison (Appendix A). Unlike Applicants assertion of several potential uses including therapies for multiple diseases Hsu et al. (2002) have indicated that HGR8 is a Relaxin receptor. In addition, porcine realxin stimulated dose-dependent c-amp production in transfected 293T cells (see Figure 1). Therefore, it does not appear that the Applicant knew the biological significance of HGR8 at the time of filing. In the absence of knowledge of the biological significance of "HGR8", there is no immediately available patentable use for it. Furthermore, the prior art of record demonstrates that the biological function of the protein family to which the disclosed protein is said to be a member is so diverse, that one could not predict which biological activity is possessed by the disclosed protein based on structural similarity alone, especially since all the members share structural similarity, but not functional similarity. To employ the instant invention in any of the disclosed methods would clearly be using it as the object of further research that has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the claimed invention, it is incomplete and, therefore, does not meet the requirements of 35 U.S.C. §101 as being useful.

It is noted in the specification that it was not possible to obtain a hybridization signal on various multiple tissue Northern blots using PCR fragment generated from the human LGR8 coding sequence as probe. The instant specification provides data on expression of the claimed message (mRNA) analyzed by PCR, indicating that it is expressed in several normal tissues (paragraph, 0372). The highest levels of LGR8 mRNA expression were detected in skeletal muscle and uterus. Lower levels were found in adrenal and testis, with lower levels still in thalamus and bone marrow. However, these disclosed properties of the claimed protein, expression pattern and potential therapeutic uses do not provide a specific, substantial and credible utility for the claimed polypeptides because there is no nexus between the expression and the diseases. The instant specification fails to teach that the claimed polypeptide is diagnostic for any specific disease. In addition, there is no correlation of the expression between normal and disease tissues. Since neither the prior art nor the specification provides for the physiological significance of the disclosed and claimed receptor, there is no immediately obvious patentable use for it.

In addition, the instant specification does not disclose a "real-world" use for said polypeptides and polynucleotides, except the prophetic recitation of potential uses, which include possible biological and therapeutic uses. Also, there are no working examples that demonstrate any specific utility. Thus, the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful. Therefore, since the peptide of the invention is not supported by a specific and substantial asserted utility or a well established utility, then the composition comprising

the polypeptide and a carrier also are not supported by a specific and substantial asserted utility or a well established utility.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7a. Claims 1-12 and 43-45 are rejected under 35 U.S.C. §112, first paragraph, as failing to adequately teach how to use the instant invention for those reasons given above in paragraph 6 with regard to the rejection of these claims under 35 U.S.C. §101.

7b. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses the nucleotides of SEQ ID NO: 1 and nucleotides encoding SEQ ID NO: 2. This meets the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose all possible allelic variants or splice variants or the various fragments or the various modifications contemplated by the Applicant. The claims as written, however, encompass variant sequences of both the nucleotide and polypeptide which were not

originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 1-3. The specification does not provide written description to support the genus encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of isolated polynucleotide of SEQ ID NO: 1 and polynucleotide encoding SEQ ID NO: 2, the skilled artisan cannot envision all the detailed chemical structure of the claimed nucleotide sequences of the variants, fragments or modifications regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the isolated polynucleotide of SEQ ID NO: 1 and polynucleotide encoding SEQ ID NO: 2 but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it

does not appear that the inventors were in possession of various polynucleotide sequences set forth in claims 1- 3.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

7c. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, even if it were enabling for SEQ ID NO: 1 and polynucleotides encoding SEQ ID NO: 2, does not reasonably provide enablement for all possible allelic variants or splice variants or the various fragments or the various modifications contemplated by the Applicant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level

of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Despite knowledge in the art for producing variants of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated with regard toallelic variants or splice variants or fragments claimed in the instant invention. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem

and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Therefore, predicting which nucleotide sequence encoding the variants would retain the functions of the LGR8 protein is well outside the realm of routine experimentation. Thus, undue amount of experimentation would be required to generate changes/modifications of the nucleotides contemplated and yet retain the function of the LGR8 variant proteins claimed.

Applicants have not taught how one of skill in the art would use the full scope of polynucleotide sequences encompassed by the invention of claims 1-3. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed sequences. The amount of experimentation required to

make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 1-3 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior at of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hsu et al. (2002). Activation of Orphan Receptors by the Hormone Relaxin. Science Vol.295, pages 671-674. This post filing reference indicates that Relaxin binds to LGR8.

9. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER